

Objective

This Progress Review of the trans-NIH Action Plan for Liver Disease Research describes progress made toward reaching the Action Plan's research goals during 2005, the first year following its release. The objective of the annual Progress Review is to aid in the implementation of the Action Plan through an ongoing assessment of progress and the need for further efforts to promote liver and biliary disease research.

Introduction

The trans-NIH Action Plan for Liver Disease Research was developed by a broad consortium of basic and clinical research investigators, physicians, health care providers and concerned lay persons, with input from the 17 Institutes and Centers at the National Institutes of Health (NIH) involved in liver disease research. The primary purpose of the Action Plan is to advance research on liver and biliary diseases with the ultimate aim of decreasing the burden of these diseases in the United States. The final document of the Action Plan summarizes the status of liver disease morbidity and mortality in the United States, the status of liver disease research, and lists 214 specific research goals for the future, with background and justification for each. The research goals are organized into 16 topic areas, and each research goal is categorized for its degree of difficulty (low, medium or high risk) and the estimated time for its completion (short, medium or long term). The final Action Plan was made available on the NIH web site (<http://liverplan.niddk.nih.gov>) in December 2004 and was published as a monograph in February 2005. The Action Plan is an ambitious and optimistic document that provides a structure and focus for research on liver and biliary diseases, which together rank among the top 10 causes of death in the United States.

The ultimate purpose of the Action Plan is to affect a decrease in the morbidity and mortality from liver and biliary diseases. The 214 research goals are focused on areas that would materially advance knowledge about liver diseases and improve means for their diagnosis, monitoring, treatment, and prevention. The research goals are specific enough to be measurable, but broad enough to affect an advance in the field.

The Action Plan document also includes plans for implementation. Attainment of the research goals is to be promoted through: (1) broad distribution of the document, (2) encouragement of its use in grant applications and in peer review, (3) promotion of collaborations between research funding entities (including industry), and (4) specific initiatives from the NIH and other Federal Agencies concerned with liver disease research, such as the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), Department of Veterans Affairs, and the Department of Defense. Primary responsibility for the Action Plan was placed on the Liver Disease Research Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Coordination of activities related to the Action Plan was the charge of the

Liver Disease Subcommittee of the statutory Digestive Diseases Interagency Coordinating Committee (DDICC).

The current document is a Progress Review of the Action Plan for the year 2005, approximately 1 year after its release. The Progress Review was prepared by the Liver Disease Research Branch with the assistance of the chairperson and members of the 16 Working Groups that initially established the research goals for the Action Plan, as well as input from members of the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee. This Progress Review provides a concise analysis of the progress made toward reaching each of the 214 goals and, when appropriate, a brief description of initiatives focusing on the specific research goal. The Progress Review is not comprehensive, but provides specific examples of important advances made in 2005 that are apropos to each research goal. Finally, the degree of progress made toward each research goal is estimated on a scale of 0 percent (no progress) to 100 percent (full attainment of the goal) in increments of 10 percent. These percentages are purely estimates but are made on the basis of agreement among experts serving on the Working Groups. The estimated degree of progress is also demonstrated graphically for each of the 16 topic areas. These assessments of progress are presented later in this document and are grouped by the 16 topic areas of the Action Plan.

The Action Plan also includes a section on Summary Recommendations, including a series of 10 overarching “benchmark” research goals. These 10 research goals are important cross-cutting goals that are mentioned in several of the 16 topic areas and would constitute clear major advances in liver disease management, control and prevention by which to assess the overall success of the Action Plan. A discussion of the status of these benchmark goals concludes this Progress Review.

Action Plan: 16 Topic Areas of Liver Disease Related Research

The titles of the 16 topic-specific chapters are listed below, along with the many individuals who contributed to this assessment of progress made toward achieving research goals in these areas. These individuals include members of the original 16 Working Groups that developed the goals, as well as others with expertise in these fields.

- **Cell and Molecular Biology of the Liver:** Drs. Allan Wolkoff, Irwin Arias, Laura Beretta, David Cohen, Anne Hubbard, Mark McNiven, Michael Nathanson, and Jose Serrano
- **Liver Injury, Inflammation, Repair, and Fibrosis:** Drs. Gregory Gores, Mark Czaja, Scott Friedman, Jacquelyn Maher, John Lemasters, Don Rockey, and Jay Hoofnagle
- **Developmental Biology and Regeneration:** Drs. Nelson Fausto, Markus Grompe, Mark Kay, George Michalopoulos, Kenneth Zaret, David Shafritz and Jose Serrano
- **Bile, Bilirubin and Cholestasis:** Drs. James Boyer, Sawkat Anwer, John Chiang, David Cohen, Norman Javitt, and Jay Hoofnagle
- **Viral Hepatitis:** Drs. Stanley Lemon, Harvey Alter, Francis Chisari, Jeffrey Glenn, William Mason, Charles Rice, Rajen Koshy, and Leonard Seeff
- **HIV and Liver Disease:** Drs. David Thomas, Margaret Koziel, Jules Levin, Marion Peters, Ken Sherman, Katherine Davenney, and Fulvia Veronese
- **Fatty Liver Disease:** Drs. Anna Mae Diehl, David Crabb, Joannes Hoek, Craig McClain, Arun Sanyal, and Sam Zakhari
- **Drug- and Toxicant-Induced Liver Disease:** Drs. Neil Kaplowitz, Timothy Macdonald, Sidney Nelson, Lance Pohl, Robert Roth, John Senior, Paul Watkins, and Carol Shreffler
- **Autoimmune Liver Disease:** Drs. John Vierling, Nora Bergasa, Nicholas Crispe, Eric Gershwin, James Gorham, Keith Lindor, Barbara Rehmann, and Stephen James
- **Pediatric Liver Disease:** Drs. Jorge Bezerra, Saul Karpen, David Perlmutter, Ron Sokol, Frederick Suchy, and Tonse Raju
- **Genetic Liver Disease:** Drs. Bruce Bacon, Nancy Andrews, Herbert Bonkovsky, Joseph Bloomer, Jonathan Gitlin, Caroline Philpott, and Alan Guttmacher
- **Liver Transplantation:** Drs. Jean Emond, Michael Lucey, Sue McDiarmid, Kim Olthoff, John Roberts, Hugo Rosen, and James Everhart
- **Complications of Liver Disease:** Drs. Thomas Boyer, Andres Blei, Michael Fallon, Roberto Groszmann, Michael Henderson, William Lee, and Leonard Seeff
- **Liver Cancer:** Drs. Adrian Di Bisceglie, Michael Abecassis, Brian Carr, Greg Gores, Snorri Thorgeirsson, Jack Wands, and Jaye Viner
- **Gallbladder and Biliary Disease:** Drs. Sum Lee, Martin Carey, Michael Kimmey, Nicholas LaRusso, Henry Pitt, and James Everhart
- **Liver Imaging and Biotechnology:** Drs. King Li, Glenn Krinsky, Jonathan Kruskal, Fred Lee, and Alan McLaughlin.

Active Initiatives in Liver Disease Research

There are several means of promoting specific areas in NIH-supported liver disease research that go beyond the focus of investigator-initiated research. The major approaches include requests for applications (RFAs), program announcements (PAs), and scientific meetings. The meetings encourage research in specific areas by bringing together experts in the field to review the current status of understanding and outline areas of specific research opportunities for the future. RFAs and PAs are published by the NIH to encourage specific areas of research. RFAs usually have a single receipt date for grant applications and set aside funds. The applications are usually reviewed by a special review group. PAs generally have multiple receipt dates that may extend over several years; the applications are typically reviewed by standard initial review groups (IRGs, also known as Study Sections), and funds are not usually specifically set aside, although these applications receive special consideration for funding. Finally, either RFAs or PAs can call for a specific type of study, consortium, database, or clinical trial focusing on an area of greatest opportunity. Table 1 lists specific PAs and RFAs released in or applicable to 2005 that encourage research applications directed at specific research goals delineated in the Trans-NIH Action Plan for Liver Disease Research.

Table 1. Program Announcements and Requests for Applications Relevant to Action Plan

| Initiative Number | Title | Sponsoring ICs |
|--|--|--------------------------|
| PAR-03-033 (Reissued as PAR-06-171) | Endoscopic Clinical Research in Pancreatic and Biliary Diseases | NIDDK, NCI |
| PA-04-043 (Reissued as PA-06-177) | Research Grants for Studies of Hepatitis C in the Setting of Renal Disease | NIDDK |
| PA-04-068 | Development of Assays for High Throughput Drug Screening | NIDDK, NCI, NIAID |
| PA-04-081 (Reissued as PA-06-185) | Proteomics: Diabetes, Obesity, and Endocrine, Digestive, Kidney, Urologic, and Hematologic Diseases | NIDDK |
| PA-04-088 (Reissued as PA-06-143) | Non-Invasive Methods for Diagnosis and Progression of Diabetes, Kidney, Urological, Hematological and Digestive Diseases | NIDDK |
| PA-05-049 | Animal Models of NIDDK-Relevant Diseases | NIDDK, NIAID |
| PAR-05-056 | Targeting Diseases Caused by Protein Misfolding or Misprocessing | NIDDK |
| PA-05-098 (Reissued as PA-06-147) | Development of Disease Biomarkers | NIDDK, NIBIB, NIAAA, ODS |
| PA-05-119 | Mechanisms of Alcoholic and Nonalcoholic Fatty Liver | NIAAA, NIDDK |
| PA-05-137 | Etiology, Prevention and Treatment of Hepatocellular Carcinoma | NCI, NIDDK, NIBIB, NIAAA |
| RFA-AI-04-028 | Hepatitis C Cooperative Research Centers | NIAID, NIDDK, NIDA |
| RFA-AT-05-006 | Phase I/II Trials of Silymarin for Chronic Liver Diseases | NCCAM, NIDDK |
| RFA-AI-05-030 | Partnerships for Hepatitis C Vaccine Development | NIAID |

The NIH also supports liver disease-related research through ongoing clinical and epidemiologic studies focused on specific diseases, procedures, and patient populations. Examples of current studies are listed in Table 2 below.

Table 2. Clinical and Epidemiologic Studies and Relevant Announcements

| Short Title/ Initiative # | Full Title | Sponsoring ICs/Agencies |
|--|--|------------------------------------|
| A2ALL | Adult-to-Adult Living Donor Liver Transplantation Cohort Study (including “LADR” study below) | NIDDK, HRSA |
| <i>LADR</i> | Low Dose Accelerating Regimen study | NIDDK, HRSA |
| AACTG | Adult AIDS Clinical Trials Group, Hepatitis Subcommittee | NIAID |
| PACTG | Pediatric AIDS Clinical Trials Group | NIAID |
| ALFSG | Adult Acute Liver Failure Study Group | NIDDK |
| PALFSG | Pediatric Acute Liver Failure Study Group | NIDDK |
| ARPKD Network | Autosomal Recessive Polycystic Kidney Disease and Congenital Hepatic Fibrosis Study | NHGRI |
| BARC | Biliary Atresia Research Consortium | NIDDK, ORD |
| CLiC | Cholestatic Liver Disease Consortium | NIDDK, ORD |
| DILIN | Drug-Induced Liver Injury Network | NIDDK, FDA |
| HALT-C | Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis trial | NIDDK, NCI, NIAID |
| HURSO | High Dose Ursodiol for Primary Sclerosing Cholangitis | NIDDK |
| LABS | Longitudinal Assessment of Bariatric Surgery | NIDDK |
| NASH CRN | Nonalcoholic Steatohepatitis Clinical Research Network (including “PIVENS” and “TONIC” below) | NIDDK, NICHD |
| <i>PIVENS</i> | Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis study | NIDDK |
| <i>TONIC</i> | Treatment of Nonalcoholic Fatty Liver Disease in Children trial | NIDDK |
| OLT HBV | Orthotopic Liver Transplantation for Hepatitis B Study | NIDDK |
| PEDS-C | Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C | NIDDK, FDA |
| PGRN | Pharmacogenetics Research Network | NIGMS |
| SPLIT | Study of Pediatric Liver Transplantation | NIDDK |
| Virahep-C | Study of Viral Resistance to Antiviral Therapy of Chronic Hepatitis C | NIDDK |
| PAR-04-078 (Reissued as PAR-06-216) | Ancillary Studies to Major Ongoing NIDDK Clinical Research Studies | NIDDK |
| PAR-04-081 | Small Clinical Grants in Digestive Diseases, Nutrition and Obesity | NIDDK |

NIH Funding of Liver Disease Research

The Trans-NIH Action Plan for Liver Disease Research provides a background that includes NIH funding levels for liver disease research through Fiscal Year (FY) 2003. Since then, funding in liver disease research has continued to grow commensurate with the growth in the overall NIH budget. The total amount of funding designated as “Liver Disease Related” for FY 2005 was approximately \$454 million, which represented an 8.4 percent increase from FY 2004—above the average NIH growth rate of 1.3 percent. The growth in Liver Disease Related research funding is shown graphically in the Figure 1 below expressed as percent growth from a baseline in 1993. The proportion of Liver Disease Related funding by NIH Institutes and Centers for FY 2005 is shown in Figure 2. The majority of funding in liver disease research continues to derive from NIDDK (38%), NIAID (19%), NCI (13%), NIAAA (8%), NIEHS (6%), NIDA (6%), NHLBI (4%), and the NCCR (3%). Another 10 NIH Institutes or Centers provide 3 percent more of the liver disease research budget.

Figure 1. Growth in Liver Disease Research Funding: FY 1993-2005

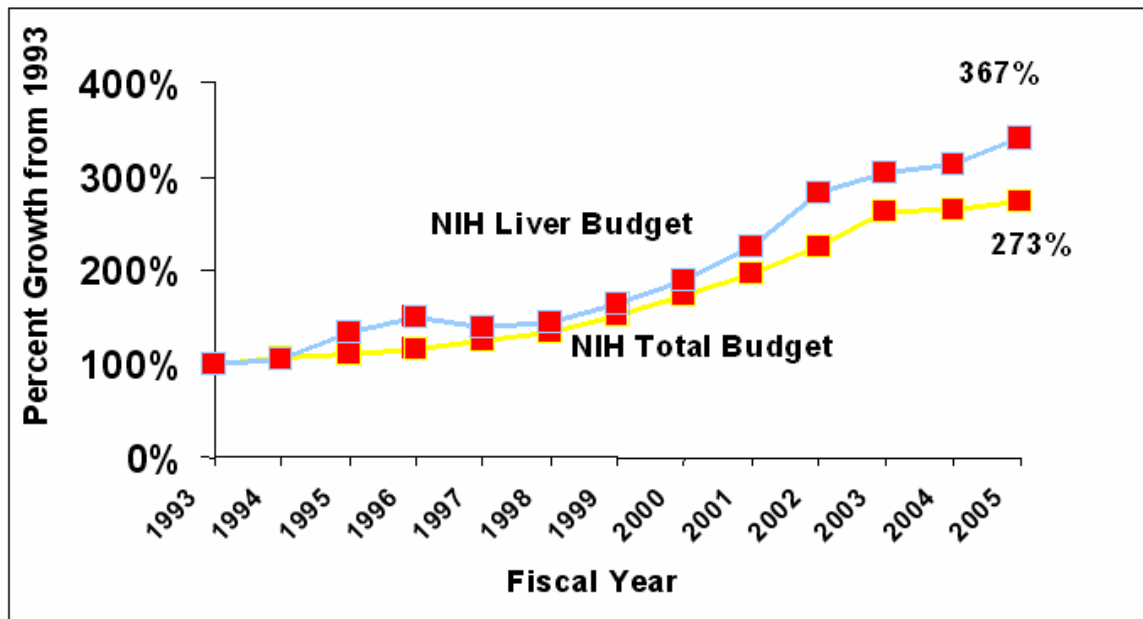
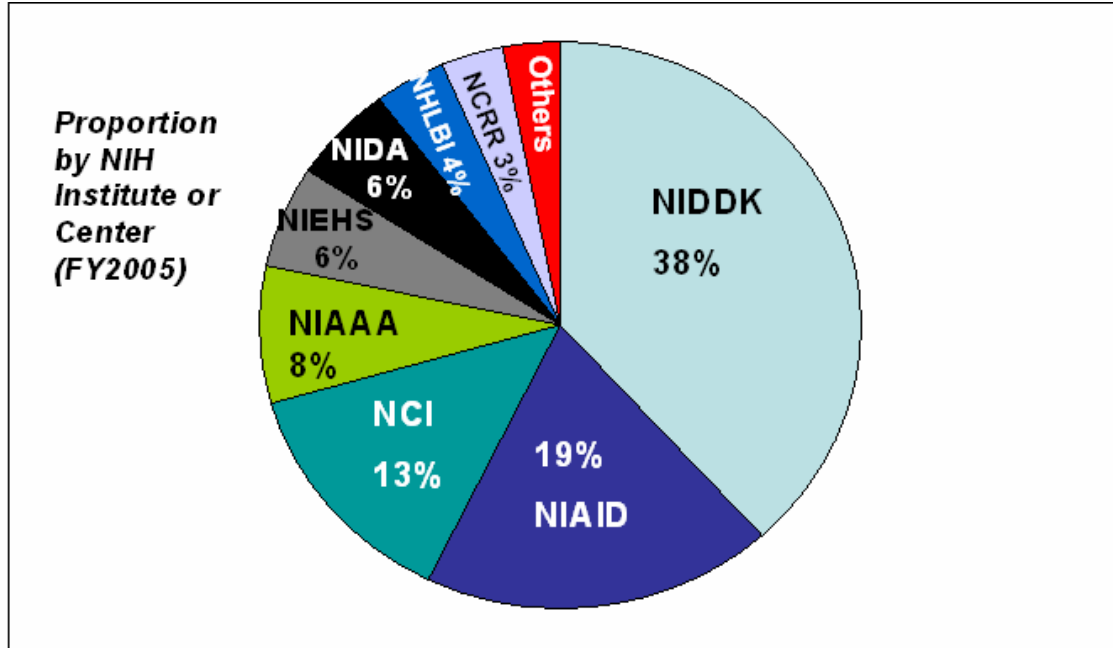


Figure 2. NIH Support of Liver Disease Related Research



Progress Review: Year One Analysis (2005)

The following 16 sections describe the first year of progress made toward reaching each of the research goals in the Action Plan's 16 topic-specific chapters, with research support provided by the NIH, other agencies, and industry. Goals are identified by the original letter-number combinations used in the Action Plan, which indicate the estimated time and degree of difficulty involved in their completion.